November 4, 2019

Mr. Julian Leichty
Office of the Environmental Health Hazard Assessment
Proposition 65 Implementation Program
P.O. Box 4010, MS-12B
Sacramento, California 95812-4010

Re: Selection of Acetaminophen for Consideration for Listing by the Carcinogen Identification Committee

Dear Mr. Leichty:

This letter concerns the California Office of Environmental Health Hazard Assessment's (OEHHA) selection of acetaminophen for consideration for listing by the Carcinogen Identification Committee (CIC) under California's "Safe Drinking Water and Toxic Enforcement Act of 1986" (also known as Proposition 65). If acetaminophen were listed as a carcinogen under Proposition 65, it is our understanding that, when sold in the State of California, a product containing acetaminophen would bear a warning stating "This product contains a chemical known to the State of California to cause cancer" (the Proposition 65 cancer warning).

I am writing on behalf of the U.S. Food and Drug Administration (FDA) to inform you that we have determined that the currently available data do not support a conclusion that exposure to acetaminophen in FDA-regulated products causes cancer. Accordingly, a Proposition 65 cancer warning on the labeling of FDA-regulated products containing acetaminophen would misbrand these products in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and, therefore, would be preempted under federal law.

To reach our conclusion, we considered the OEHHA document *Proposition 65: Evidence of the Carcinogenicity of Acetaminophen* (September 2019), reconsidered the historical record supporting current carcinogenicity and mutagenicity labeling on prescription acetaminophen, and reviewed the clinical epidemiologic literature through April 2019. A summary of our assessment follows.

1. FDA Labeling History

Acetaminophen was first approved as a prescription drug by the FDA in 1950 and has also been available for nonprescription over the counter (OTC) use since 1955 (20 FR 3499; May 19, 1955). FDA revised the carcinogenesis and mutagenesis sections of prescription acetaminophen professional labeling during the review of NDA 22-450, Ofirmev® (acetaminophen) injection, 10 mg/mL, which was approved November 2, 2010. To support that application, the FDA requested that the Applicant submit a literature review and propose revised labeling to update key nonclinical portions of the labeling. FDA reviewed the published literature submitted and conducted its own review of the existing literature to update the drug product labeling. The redacted pharmacology toxicology reviews of the NDA are publicly available.[1]

During that review, the FDA noted that the World Health Organization's International Agency for Research

[1] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022450Orig1s000PharmR.pdf

on Cancer (IARC) last evaluated the carcinogenic potential of acetaminophen (also known as paracetamol) in 1999 and concluded that there was "*inadequate evidence* in humans for the carcinogenicity of paracetamol" (emphasis original) and that there was "*inadequate evidence* in experimental animals for the carcinogenicity of paracetamol" (emphasis original) (IARC 1999). IARC's overall evaluation was that "[p]aracetamol is *not classifiable as to its carcinogenicity to humans* (Group 3)." As described in the preamble to the IARC monograph, the category Group 3 is assigned to compounds "for which the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals." The term inadequate evidence is also defined by IARC to mean that "the available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available."

The FDA's review of the literature noted that, although there were several published nonclinical reports describing the potential carcinogenic effects of acetaminophen (Flaks and Flaks 1983; Hiraga and Fujii 1985), the most comprehensive studies available to date and the only studies available that included sufficient detail to permit substantive independent review were those completed by the U.S. National Toxicology Program (NTP) (National Toxicology Program 1993). The NTP studies, which were conducted in accordance with Good Laboratory Practices (GLPs), examined the carcinogenic potential of acetaminophen in F344/N rats and B6C3F1 mice in 2-year dietary studies. The report conclusion states that "[u]nder the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity* of acetaminophen in male F344/N rats that received 600, 3,000, or 6,000 ppm. There was *equivocal evidence of carcinogenic activity* of acetaminophen in female F344/N rats based on increased incidences of mononuclear cell leukemia. There was *no evidence of carcinogenic activity* of acetaminophen in male and female B6C3F1 mice that received 600, 3,000, or 6,000 ppm" (emphasis original). As described in the report, the NTP definition of equivocal evidence is as follows: "Equivocal evidence of carcinogenic activity describes studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related."

Noting the equivocal findings reported by the NTP studies, the FDA further reviewed and discussed the findings. As noted in the NTP report, arguments against an association of acetaminophen and mononuclear cell leukemia (MNCL) in female rats included the lack of a signal in the male rats, the variability of the background rates for this finding in Fischer rats, and the lack of concordance with a lifetime study of acetaminophen in Fischer rats in a study conducted in Japan. It is important to note that NTP has not used the F344/N rat strain since 2006 for a variety of reasons, including a high incidence of MNCL, a disorder to which F344/N rats are susceptible but for which there is no clear human counterpart. (King-Herbert A and Thayer K 2006; Maronpot et al., 2016).

Based on the FDA's review of the NTP studies, the following statement was included in the Ofirmev® labeling:

<u>*Carcinogenesis*</u>
Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 0.8 times the maximum human daily dose (MHDD) of 4 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats (0.7 times) or

mice (1.2-1.4 times the MHDD, based on a body surface area comparison).

The FDA also reviewed submitted studies and published data characterizing the genotoxic potential of acetaminophen, which have reported mixed results. The current labeling reflects the results of the GLP studies submitted to NDA 22-450 and the results of the studies conducted by NTP. The labeling states the following:

Mutagenesis

Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, acetaminophen tested positive in the in vitro mouse lymphoma assay and the in vitro chromosomal aberration assay using human lymphocytes. In the published literature, acetaminophen has been reported to be clastogenic when administered a dose of 1500 mg/kg/day to the rat model (3.6 times the MHDD, based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (1.8 times the MHDD, based on a body surface area comparison), suggesting a threshold effect.

2. Nonclinical Assessment

Of the nonclinical carcinogenicity studies published to date, FDA considers the rat and mouse studies completed by NTP to be the most reliable studies because the studies were conducted in accordance with GLPs and include adequate detail to permit substantive independent review. These studies conclude that acetaminophen did not result in evidence of carcinogenicity in male F344/N rats or male or female B6C3F1 mice. The NTP concluded in 1993 that there were equivocal findings in female F344/N rats based on an increased incidence of MNCLs in the high-dose animals. However, in 1999 IARC concluded that the finding was not treatment related given the background incidence of MNCLs in this strain. In 2010 the FDA's Executive Carcinogenicity Assessment Committee (ECAC) review concluded that these findings are of limited human relevance for the same reason.

We note that the NTP discontinued use of the F344/N strain of rats for carcinogenicity testing in 2006 due to several reasons, including the observation that the colony had a high background incidence of certain tumors including MNCLs, as well as Leydig cell tumors, and tunica vaginalis mesothelioma (King-Herbert and Thayer, 2006; King-Herbert et al., 2010). As noted in a recent review, the incidence of MNCLs in the colony progressively increased since the 1970s, contributing to early mortality and necessitating the need for multiple historical control datasets for interpretation of the study results. Furthermore, evaluation of the study requires consideration that the agent being tested may increase the incidence of background MNCLs (Maronpot et al., 2016). Maronpot et al. conclude that the MNCLs in F344/N rats lack a human counterpart and should not be used to assess potential human health hazards (Maronpot et al., 2016).

Review of the OEHHA cited publications confirms the FDA's previous conclusion that the only studies that contain adequate data to permit substantive independent review of the findings are the studies completed by NTP. Although published nonclinical studies report occasional increased incidence of tumor findings, the findings do not appear to be reproducible, occurred only in tissues with significant histopathology, or were in uncommon strains of animals with limited historical control data. Collectively these studies do not provide clear evidence of carcinogenicity in animals.

Although we agree that the mechanistic data reviewed by OEHHA support the biological plausibility for a potential role of acetaminophen in tumorigenesis, the net impact of the key characteristics of acetaminophen identified were tested by the NTP in the two-year nonclinical studies in mice and rats to assess the carcinogenic potential of acetaminophen. No clear treatment-related tumors were identified. While we acknowledge that the California OEHHA report concludes that mechanistic data for acetaminophen meet four of the "10 Key Characteristics of Carcinogens," application of the 10 Key Characteristics has not been fully validated, and results from adequate carcinogenicity studies carry more weight than a mechanistic evaluation.

From a nonclinical pharmacology toxicology perspective, although acetaminophen has the potential to produce significant hepatotoxicity and renal toxicity, particularly if glutathione levels are depleted, there are no new nonclinical data to change our previous conclusions regarding the carcinogenic potential of this compound. The existing nonclinical data are inadequate to support a conclusion that acetaminophen is an animal carcinogen.

3. Clinical Assessment

The IARC last evaluated the carcinogenic potential of acetaminophen in 1999 and concluded that there was "*inadequate evidence* in humans for the carcinogenicity of paracetamol" (emphasis original). Since then, several epidemiologic studies evaluating whether there is an association of various cancers with acetaminophen exposure have been published. We are not aware of any randomized clinical trials that assess whether acetaminophen has carcinogenic potential.

FDA conducted a systematic review of the available epidemiologic evidence since 1999 and we have determined that the currently available evidence does not support a conclusion that exposure to acetaminophen in FDA-regulated products causes cancer.

Acetaminophen exposure was not associated with most cancer sites studied and in a few studies was inversely associated with certain cancers. FDA concurs, therefore, with OEHHA's assessment that, for the majority of cancers assessed (i.e., breast, ovary, uterine endometrium, prostate, skin, colorectum, brain, respiratory tract, gastrointestinal tract, pancreas, cervix, and all cancers combined), use of acetaminophen was associated with decreased, null, or inconsistent cancer risk or data were too sparse to evaluate.

Some studies reported an association between acetaminophen exposure and increased risk of cancers of kidney, urinary bladder, urinary tract, lymphohematopoietic system, and liver. However, important methodological limitations, as discussed below, limit interpretability of the findings. The discussion below focuses on important methodological concerns affecting most studies, namely exposure misclassification, confounding, and protopathic bias, followed by a discussion of the evidence according to specific cancer site.

Acetaminophen Exposure Misclassification

Acetaminophen is identified as either a first-line or preferred OTC pain relief option by multiple professional societies, including the American Heart Association; National Kidney Foundation; American Geriatrics Society; American College of Gastroenterology; American College of Rheumatology; and American College of Emergency Physicians (Antman et al. 2007; National Kidney Foundation; American

Geriatrics Society 2009; American College of Gastroenterology; Hochberg et al. 2012; American College of Emergency Physicians 2017).

The utility of acetaminophen as an effective pain and fever reliever has resulted in its ubiquity in the United States market. Most adults at one time or another have likely been exposed to acetaminophen, making the identification of a non-exposed control group challenging. According to The Slone Survey, acetaminophen is the most commonly used pain and fever drug in the United States, mostly short-term, although 23% of adults in the United States use it weekly (Kaufman et al. 2002). It is available in numerous prescription and OTC single and combination ingredient drug products.

Inability to accurately capture acetaminophen exposure is an important limitation of the epidemiologic studies reviewed. Study definitions of exposed subjects ranged from not reported to specified use per day, week, month, or year of OTC and/or prescription acetaminophen, which complicates cross-study comparisons. In addition, determining exposure to an ingredient that is widely available in multiple products with different brand names and uses is a challenge for observational studies. For combination or brand name products especially, consumers and patients may not realize a product contains acetaminophen. Recall over long periods of time can be especially challenging. Misclassification related to exposure is a substantial limitation of the available data.

Confounding

Unmeasured or residual confounding and bias are always possible explanations for findings from observational studies. As most acetaminophen is taken on an as needed basis, bias from misclassification of exposure and recall is a concern in observational studies. There may also be intrinsic differences between participants taking acetaminophen on regular basis and those who do not. Channeling bias is also a potential concern, as acetaminophen is sometimes preferentially recommended to patients with a history of gastrointestinal bleeding, myocardial infarction, stroke, renal disease, allergy, asthma, and other conditions. Weinstein et al. examined whether evidence of channeling bias exists in observational studies that compare acetaminophen with ibuprofen, and, if so, the extent to which statistical adjustment can mitigate this bias (Weinstein RB et al. 2017). As participants with history of renal disease were more likely to receive a prescription for acetaminophen (7.4%) than ibuprofen (2.8%), bias from selective prescribing cannot be ruled out.

Protopathic Bias

Another potential bias is protopathic bias, which occurs when the initiation of a drug occurs in response to a symptom of the undiagnosed disease under study. Pain and fever are common symptoms of cancer, for which undiagnosed individuals may use acetaminophen.

Kidney Cancer

OEHHA has assessed the association between acetaminophen and kidney cancer in four cohort studies, two nested case-control studies, 12 publications from case-control studies, and two meta-analyses. This included 12 case-control studies of renal cell carcinoma (RCC) and four of the renal pelvis. As stated in the OEHHA report, the case-control studies generally reported non-statistically significant increases in renal cell carcinoma (RCC) and cancer of the renal pelvis. The most informative studies were the nested

case-control studies by Derby and Jick (1996) and Kaye et al. (2001) and two largest case-control studies (Gago-Dominguez et al. 1999; Karami et al. 2016) and the pooled analysis of case-control studies (McCredie et al. 1995). The FDA reviewed these studies and noted important methodological limitations.

The 1999 IARC assessment reviewed studies by Derby and Jick (1996) as well as McCredie et al. (1995) and concluded there was "*inadequate evidence* in humans" (emphasis original) for carcinogenicity. Of three other studies, Kaye et al. (2001) prospectively evaluated prescription acetaminophen using medical records; Karami et al. (2016) defined regular OTC use as ≥1 x/week for ≥3 months ≥2 years prior; and Gago-Dominguez et al. (1999) evaluated prescription and OTC use ≥2 x/week for ≥1 month using a visual aid to assist recall. Odds ratios (OR) ranged from 1.35 for ever use (Karami et al. 2016) to 2.3 for ≥20 prescriptions (Kaye et al. 2001). However, concerns regarding potential channeling bias, confounding/residual confounding and exposure misclassification cannot be ruled out.

Urinary Bladder Cancer

OEHHA assessed three cohort studies, two nested case-control studies, and six case-control studies that examined the association of acetaminophen with bladder cancer. The case-control studies had a mix of positive and null findings. The three most informative studies assessed acetaminophen use prospectively using medical records. Friis et al. (2002) and Kaye et al. (2001) reported non-significant increased risk of bladder cancer with low to moderate use and no dose-response trend. Derby and Jick (1996) reported a non-statistically significant increase with high use. None of the three most informative studies reported a statistically significant increase in the risk of urinary bladder cancer.

The 1999 IARC assessment reviewed Derby and Jick (1996), and Kaye et al. (2001) as discussed above. Regarding Friis et al. (2002), OTC use was not collected nor were data on analgesic use prior to the start of the prescription database, compliance with the medication, and the indication for its use. Friis et al. indicated that their results might have been confounded by smoking and alcohol use, which they noted are associated with analgesic use.

Urinary Tract Cancer

OEHHA assessed two cohort and six case-control studies that evaluated the association between acetaminophen use and other urinary tract cancers or combined urinary tract sites (i.e., three studies of renal pelvis and ureter; two studies of transitional cell carcinoma (TCC) that included multiple urinary tract sites; and one study of ureter cancer). Cohort studies of urinary tract cancer (Friis et al. 2002; Walter et al. 2011a) did not demonstrate significant increases in risk. Results of case-control studies were inconsistent (Steineck et al. 1995; Rosenberg et al. 1998); both were included in the IARC's 1999 assessment along with McCredie and Stewart (1988). Hence, there were no informative studies of the association of acetaminophen use with urinary tract cancer.

Lymphohematopoietic System Cancer

Hematologic malignancies are distinctive disorders and the pathogenesis of these disorders is a complex process that is not the same across the various hematologic malignancies. The FDA does not recommend grouping hematologic malignancies when evaluating for potential risk factors. The evaluation should occur at the individual disease level.

Maternal acetaminophen use was not associated with childhood acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) or acute leukemia with mixed-lineage leukemia 1 (MLL) rearrangements (Ognjanovic et al. 2011; Couto et al. 2015).

Regarding adult leukemias in more recent studies, a case-control study by Ross et al. (2011) reported non-significant association with chronic myeloid leukemia and a statistically significant increase in AML in women but not men. Weiss et al. (2006) demonstrated non-statistically significant positive associations for ALL and AML.

Regarding Non-Hodgkin Lymphoma (NHL), Baker et al. (2005) reported on NHL and its cellular subtypes – diffuse large B-cell lymphoma (DLBCL), follicular, small lymphocytic leukemia/chronic lymphocytic leukemia (SLL/CLL), and T-cell lymphoma. Baker et al. (2005) demonstrated that regular acetaminophen use was associated with elevated NHL risk among women (aOR 1.71; 95% CI, 1.18-2.5) but not among men (aOR 0.75, 95% CI, 0.48-1.17). Kato et al. (2002) did not find a statistically significant increased risk of NHL with three or more years of acetaminophen use. The cohort Vitamins and Lifestyle (VITAL) study by Walter et al. (2011) showed a statistically significant increase in mature B-cell neoplasms other than CLL/SLL or plasma cell disorders (HR 1.81; 95% CI 1.1-2.93), plasma cell disorders (HR 2.42; 95% CI 1.08-5.41), and myeloid neoplasms (HR 2.26; 95% CI 1.24-4.12). However, we note important limitations including low response rates and potential misclassification of exposure.

Regarding multiple myeloma, results are inconsistent. The Danish cohort study by Friis et al. (2002) did not find a statistically significant increased risk associated with prescription use (SIR 1.6; 95% CI 0.6-3.2). The hospital-based case-control study by Moysich et al. (2007) suggested a significant increase in multiple myeloma with regular use (i.e., ≥1/week for ≥6 month) and long-term use (>10 years), with odds ratios among the highest seen in the cancer studies (i.e., OR 2.95 (95% CI 1.72-5.08) and OR 3.26 (95% CI 1.52-7.02) for regular and >10 years of use, respectively). Important limitations include small sample size, potential biases inherent to hospital-based studies, and the timing of exposure that could have overlapped with prodromal symptoms, although the latter is less likely to explain the observed association among participants with longer duration of exposure.

An association between acetaminophen exposure and risk of Hodgkin Lymphoma was evaluated in the case-control study by Chang et al. (2004). Although the study demonstrated a significant increase in risk with regular use (i.e., ≥2 x/week), the authors stated that the increased risk is more likely explained by uncontrolled confounding factors than by a true association.

Liver Cancer

OEHHA assessed the association between acetaminophen use and liver cancer in two large independent cohorts that assessed acetaminophen use through prescription databases – one from Denmark (Friis et al. 2002; Lipworth et al. 2003) and one from the United Kingdom (McGlynn et al. 2015; Yang et al. 2016). Friis et al. (2002) did not find a significant association of prescription acetaminophen with liver cancer (SIR 1.8; 95% CI 0.7-3.6). The liver cancer mortality findings in Lipworth et al. (2003) were inconsistent between men and women. The Danish cohort had the limitation that it could not control for confounders such as smoking and alcohol use.

Yang et al. (2016) is a case-control study conducted within the United Kingdom's Clinical Practice Datalink, which contains prospectively collected prescription medicines and clinical diagnoses. With use of 0-1 prescriptions as the reference group, use of ≥2 prescriptions was weakly associated with liver cancer (OR 1.18; 95% CI 1.00–1.39) with multiple adjustments. The index date was defined as one year prior to diagnosis, and current use was defined as use within one year prior to the index date. However, OTC use was not considered and it is possible that residual confounding or other biases may explain the small observed odds ratios Current use with a total of ≥40 prescriptions showed the highest risk estimate (adjusted OR 1.51; 95% CI 1.15–1.99); however, use of ≥40 prescriptions ending more than one year before the index date did not show a risk (adjusted OR 1.06; 95% CI 0.47–2.39). The authors note that this could indicate reverse causality, to the extent patients were taking analgesics because of early symptoms of liver cancer. A subgroup analysis showed that the association with liver cancer was present only in subjects with Body Mass Index < 25 kg/m2, for reasons that were not apparent.

Clinical Summary

The clinical review of the OEHHA-cited publications confirms the FDA's previous conclusion that available data do not support a conclusion that exposure to acetaminophen in FDA-regulated products causes cancer. For the majority of cancers assessed (i.e., breast, ovary, uterine endometrium, prostate, skin, colorectum, brain, respiratory tract, gastrointestinal tract, pancreas, cervix, and all cancers combined), use of acetaminophen was associated with decreased, null, or inconsistent cancer risk or data were too sparse to evaluate. Cohort and case-control data pertaining to cancers of the kidney, urinary bladder, urinary tract, lymphohematopoietic system, and liver are subject to substantial limitations - specifically potential biases regarding sub-optimal capture of acetaminophen exposure, channeling/confounding, and residual confounding. Further, results were inconsistent and varied by malignancy evaluated, study design, exposure, and gender. We are not aware of any randomized clinical trials that assess whether acetaminophen has carcinogenic potential. In sum, we find substantial limitations in the available clinical data assessing the carcinogenic potential of acetaminophen, and the nonclinical data do not support a conclusion that acetaminophen is a carcinogen.

4. Benefit and Risk Considerations

Millions of Americans rely on acetaminophen as a non-opioid treatment for their pain. According to the Centers for Disease Control and Prevention, 50 million adults in the United States have chronic daily pain, with 19.6 million adults experiencing high-impact chronic pain that interferes with daily life or work activities. (U.S. Department of Health and Human Services (2019)). The effectiveness of acetaminophen in temporarily reducing fever and relieving minor aches and pains has been demonstrated in clinical trials.

Currently available evidence supports a conclusion that exposure to acetaminophen under certain circumstances may increase risk of liver damage (74 FR 19385). In contrast, we do not find that currently available nonclinical and clinical data support a conclusion that such exposure causes cancer. We are concerned, too, about the unintended risks of adding an unjustified warning to labeling. A carcinogenicity warning for acetaminophen may drive patients who are doing well on acetaminophen to other pain relievers, each of which has its own risk profile. An increase in opioid use would be especially concerning. We therefore do not think a warning would be in the best interests of public health.

5. Preemption Under Federal Law

As described above, FDA has determined that the currently available evidence does not support a conclusion that acetaminophen in FDA-regulated products causes cancer. Accordingly, a Proposition 65 cancer warning on the labeling of products containing acetaminophen would not be scientifically accurate, and such labeling would be false or misleading. Specifically, this warning could mislead consumers into believing that using a drug product containing acetaminophen would increase their risk for developing cancer. Such a misleading warning on a drug product's labeling would render the product misbranded under the FD&C Act. *See* FD&C Act section 502(a), 21 U.S.C. §352(a) (stating that a "drug or device shall be deemed to be misbranded" if its labeling is "false or misleading in any particular"); *see also National Ass'n of Wheat Growers v. Zeise*, 309 F. Supp. 3d 842, 851 (E.D. Cal. 2018) (stating that where numerous government agencies and health organizations have found no evidence that a chemical causes cancer, a Proposition 65 cancer warning would be "misleading at best" because "the most obvious reading of the Proposition 65 cancer warning is that exposure to [the chemical] in fact causes cancer").

When a Proposition 65 cancer warning mandated by California law directly conflicts with FDA's conclusion that such warning would render a product's labeling false or misleading in violation of the FD&C Act, the Proposition 65 warning is preempted under federal law. *See Crosby v. Nat'l Foreign Trade Council*, 530 U.S. 363, 372 (2000) (noting "state law is naturally preempted to the extent of any conflict with a federal statute," including "where it is impossible for a private party to comply with both state and federal law"); *see also PLIVA, Inc. v. Mensing*, 564 U.S. 604, 617-18 (2011) (finding in the context of generic drug labeling that federal law preempts any state law that would require a warning rendering a product misbranded under the FD&C Act).[2] Accordingly, a Proposition 65 cancer warning for drug products containing acetaminophen would be preempted under federal law.

We would be happy to discuss these issues further.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration

[2] The California Supreme Court has concluded that although language in the FD&C Act exempts Proposition 65 from the application of express preemption for the labeling of OTC drugs (see section 751 of the FD&C Act, 21 U.S.C. § 379r), the doctrine of implied conflict preemption still applies. *See Dowhal v. SmithKline Beecham Consumer Healthcare*, 32 Cal. 4th 910, 919-29 (Cal. 2004).

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